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Are Complementary Therapies and Integrative Care Cost-Effective? A Systematic Review of Economic Evaluations

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Economics of complementary and integrative medicine

Abstract

Objective. A comprehensive systematic review of economic evaluations of CIM to establish the value of these therapies to health reform efforts.

Data sources. PubMed, CINAHL, AMED, PsychInfo, Web of Science, and EMBASE were searched from inception through 2010. In addition, bibliographies of found articles and reviews were searched, and key researchers contacted.

Eligibility criteria for selecting studies. Studies of CIM were identified using criteria based on those of the Cochrane CAM group. All studies of CIM reporting economic outcomes were included.

Study appraisal methods. All recent (and likely most cost-relevant) full economic evaluations published 2001-2010 were subjected to several measures of quality. Detailed results of higher-quality studies are reported.

Results. A total of 338 economic evaluations of CIM were identified, of which 204, covering a wide variety of CIM for different populations, were published 2001-2010. 114 of these were full economic evaluations. 90 percent of these articles covered studies of single CIM therapies and only one compared usual care to usual care plus access to multiple licensed CIM practitioners. Of the recent full evaluations, 31 (27%) met five study-quality criteria, and 22 of these also met the minimum criterion for study transferability ("generalizability"). Of the 56 comparisons made in the higher-quality studies, 16 (29%) show a health improvement with cost savings for the CIM therapy versus usual care. Study quality of the cost-utility analyses (CUAs) of CIM was generally comparable to that seen in CUAs across all medicine according to several measures,

and the quality of the cost-saving studies was slightly, but not significantly, lower than those showing cost increases (85% versus 88%, p=.460).

Conclusions. This comprehensive review identified many CIM economic evaluations missed by previous reviews and emerging evidence of cost-effectiveness and possible cost savings in at least a few clinical populations. Recommendations are made for future studies.

Article summary

Article focus

- Given the limited nature of previous systematic reviews, what is the extent of evidence on the economic impacts of complementary and integrative medicine (CIM)?
- What are the range of therapies and populations studied, and the quality of published economic evaluations of CIM?
- What are the results of the higher-quality, more recent (and likely most cost-relevant) economic evaluations of CIM?

Key messages

- This study's comprehensive search strategy identified 338 economic evaluations of CIM, including 114 full evaluations published 2001-2010.
- The cost-utility analyses found were of similar or better quality to those published across all medicine.
- The higher-quality studies indicate potential cost-effectiveness, and even cost savings across a number of CIM therapies and populations.

Strengths and limitations of this study

- The strengths of this study are the comprehensive search strategy, the use of two reviewers, the use of multiple measures of study quality, and the identification of higher-quality studies, for which results are reported in detail, via an objective short-list of quality criteria, which reduced the potential for bias.
- The weaknesses of this study are similar to those of the other systematic reviews: reviewers were not blinded to journals and article authors, and some aspects of what makes a quality economic evaluation could not be judged from what was reported.
- Publication bias was not assessed. However, it is not clear whether publication bias is relevant given the purposes of this review.

Introduction

Between 1990 and 2007, four nationally representative surveys demonstrated that a third or more of US adults routinely used complementary and alternative medicine (CAM) therapies to treat their principal medical conditions.[1-4] Total expenditures for CAM therapies were estimated at $14 Billion in 1990,[1] $27 Billion in 1997,[2] and $34 Billion in 2007.[4] The 2007 US National Health Inventory Survey found that out-of-pocket expenditures for CAM therapies accounted for 11 percent of all out-of-pocket health care expenditures by Americans.[4] Similar use numbers are seen in other countries.[5-8] However, despite the popularity of and substantial expenditures on CAM therapies, their cost effectiveness remains ill-defined and controversial.

Economic evaluations allow costs to be included, alongside data on safety and effectiveness, in healthcare policy decisions. As healthcare costs rise, the availability of these economic evaluations becomes increasingly important to the formulation of disease management strategies which are both clinically effective and financially responsible. According to the National Center for Complementary and Alternative Medicine (NCCAM), complementary and alternative medicine (CAM) is "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine."[9] In not being part of conventional medicine, individual complementary therapies and emerging models of integrative medicine (i.e., coordinated access to both conventional and complementary care)—collectively termed complementary and integrative medicine (CIM)—are often excluded in financial mechanisms commonly available for conventional medicine,[2] and are rarely included in the

range of options considered in the formation of healthcare policy. The availability of economic data could improve the consideration and appropriate inclusion of CIM in strategies to lower overall healthcare costs. In addition, economic outcomes are relevant to the licensure and scope of practice of practitioners, industry investment decisions (e.g., the business case for integrative medicine), consumers, and future research efforts (i.e., through identifying decision-critical parameters for additional research[10]).

A number of systematic reviews of economic evaluations of CIM have been published.[11-23] Five of these prior reviews attempted to capture all economic evaluations of CIM therapies across all conditions.[11 19-21 23] However, it is unclear whether all or even the majority of economic evaluations of CIM have been identified by these reviews. The searches are dated; the search strategy in the most recent review only captured articles published through 2007.[23] The databases searched were limited—e.g., only one used CINAHL,[21] and only two others used EMBASE,[19 23] both in addition to Medline and AMED. Finally, these reviews generally used limited search terms to identify CIM studies. All but one only used variations on the terms "complementary" or "alternative" "medicine" or "therapy". Unfortunately, other reviewers have found that these search terms do not capture all CIM studies,[24 25] which may be a reflection of the difficulty in defining what is and is not CIM.[26] The search by Maxion-Bergemann and others[11] also added individual therapies as search terms, but only included homeopathy, phytotherapy, Traditional Chinese Medicine, anthroposophic medicine, and neural therapy. No search included "integrative medicine."

The goal of this paper is to identify, to the extent possible, all published economic evaluations of complementary and integrative medicine (CIM), describe the types of CIM evaluated and the clinical conditions for which they have been evaluated, and identify the more recent (and therefore, most cost-relevant) higher-quality studies and highlight their results for policy makers. We also make recommendations for future economic evaluations of CIM.

Methods

Six electronic databases were searched from their inception through December 2010: PubMed, CINAHL, AMED, PsychInfo, Web of Science, and EMBASE. To be as comprehensive as possible, a combination of 11 medical subject heading (MeSH) and 39 other search terms were used (see Box 1). In addition, bibliographies of found articles and reviews were searched, and key researchers in various areas of CIM were contacted for their lists of known studies. Although non-English language articles were collected, they are not analyzed in this review.

Box 1. Search terms used: (Complementary Therapies [MeSH], Dietary Supplements [MeSH], Micronutrients [MeSH], Trace Elements [MeSH], Vitamins [MeSH], acupuncture, alternative medicine, ayurvedic medicine, chiropractic, biofeedback, collaborative medicine, complementary and alternative medicine, botanical medicine, complementary medicine, diet, energy medicine, herbal medicine, herbs, homeopathy, hypnosis, integrated medicine, integrative medicine, massage, meditation, mind-body medicine, minerals, naturopathic medicine, naturopathy, nutrients, nutritional supplements, relaxation, spa therapy, traditional Chinese medicine, OR vitamins) AND (Cost-Benefit Analysis [MeSH], Cost Control [MeSH], Cost Savings [MeSH], Costs and Cost Analysis [MeSH], Economics [MeSH], economics

[Subheading], Insurance [MeSH], cost benefit, cost effectiveness, cost identification, cost minimization, cost utility, economic evaluation, insurance claims, managed care, OR technology assessment). The search was restricted to human studies.

Defining a comprehensive search strategy for CIM is challenging.[24 27-29] There have been a number of efforts to develop a concise definition of CAM.[26 30] This review used the one developed by the members of the Cochrane CAM Field[31] and then added the terms "integrative," "integrated," and "collaborative" medicine. The Cochrane CAM definition starts with the NCCAM definition[9] and then refines it by specifically including all therapies "based upon the theories of a medical system outside the Western allopathic medical model" (e.g., traditional Chinese medicine, Reiki), and including others depending on the context and setting of their use. The context of use considers treatment/condition combinations and excludes those "currently considered to be standard treatment," and the setting of use generally includes self-care and therapies delivered by CIM providers, but excludes therapies "delivered exclusively by conventionally-credentialed medical personnel or exclusively within hospital settings." Therefore, therapies such as chemotherapy regimens (e.g., chronotherapy[32]), and therapies requiring surgical implantation (e.g., neuroreflexotherapy[33]) or the placement of a feeding tube[34] were not included even though these therapies appeared in our search. In cases where CIM therapies (e.g., biofeedback or hypnosis) were included as part of a package of care (e.g., with cognitive behavioral therapy), a judgment was made as to whether the CIM portion of the treatment made up half or more of the overall package of care under study. If so, the package of

care was included as CIM. Because more than half of CIM users use multiple CIM therapies,[35] studies of packages of therapies and coordinated care were identified as such.

Articles were categorized as full economic evaluations if they compared both the costs (inputs) and consequences (economic, clinical, and/or humanistic outcomes[36]) of two or more therapeutic alternatives applied to the same patient population.[37, p11] Otherwise, they were considered partial evaluations, e.g., cost-identification or cost-comparison studies.[38] Studies that estimated resource utilization were included as economic evaluations if the utilization data were detailed enough to allow monetary valuation.

Two reviewers (PMH and BLP) evaluated all articles for inclusion and extracted all data. Disagreements were resolved by discussion between the two review authors, or, if needed, by the other co-authors. Because the results of economic evaluations can rapidly lose relevance with time, mainly due to changes in practice patterns and cost structures, data were extracted only from the economic evaluations published 2001 through 2010. Extracted data were entered into an Excel template developed for a previous review.[20] The type(s) of CIM evaluated and the target population were captured for all economic evaluations. Various indicators of study quality were captured for all full economic evaluations, and more detailed data and results were captured only for those full economic evaluations that met five quality criteria.

The quality of an economic evaluation can be judged along two general dimensions: 1) whether the study was a quality measure of outcomes for its target population and location—i.e., whether it was internally valid; and 2) whether enough information is provided for the study's results to

be transferable ("generalizable").[39] Health outcomes are to some extent considered generalizable across settings, however, because resource availability, practice patterns and relative prices can vary greatly, economic outcomes are usually not.[40] Therefore, one goal in economic evaluation is to ensure the *transferability* of study results—i.e., to provide enough study detail so that results can be adapted (usually via modeling) to apply to other settings.[39] The 35-item *BMJ* checklist captures components of both dimensions of quality and was applied to all full economic evaluations.[41] We also chose five quality criteria by which to identify a subset of full economic evaluations to highlight as being of most interest to policy makers. These quality criteria are based on recommendations made by the US Panel on Cost Effectiveness in Health and Medicine [42] and by well-known experts in the field,[37] and focus on the quality of the underlying study (the first type of quality):

- Because cost effectiveness analysis is comparative, to ensure that results are useful to decision makers, one of the alternatives to which the CIM intervention was compared must be some version of commonly available (routine, standard or usual) care.
- The analysis must explicitly or implicitly use (and include all relevant costs from) at least one recognized perspective—e.g., society, third-party payer, hospital, or employer.
- Since "an economic evaluation of a health care programme is only as good as the effectiveness data it is built upon,"[43, p232] health outcomes must be from randomized controlled trials or non-randomized controlled trials using either statistical adjustment or matching to address baseline differences.

- Since having patient-specific data on both costs and outcomes is an advantage for internal validity,[44] resource use must be a measured outcome of the study. Modeling studies utilize the results of other published studies, therefore, are exempt from this criterion.
- Because uncertainty in an economic evaluation comes not just from sample variation, but also from assumptions made,[45] a sensitivity analysis is required.

Because the prices used to value resources are highly location- and setting-specific,[39 46] we also note, for the articles meeting the above criteria, the presence of a study reporting criterion essential for the transferability of study results (usually via modeling):[39 40] separate reporting of unit costs from resource use for economic evaluations alongside trials, or from model parameters (e.g., transition probabilities) for economic evaluations using models.

Other data extracted for the economic evaluations which meet the five study-quality criteria are: treatment and study duration, primary clinical and economic outcome measures, the setting in which treatment took place, study design and sample size, the type (see Table 1) and perspective (i.e., the point of view used to define costs) of the economic analysis, and incremental cost-effectiveness of the CIM alternative compared to usual care. Incremental cost-effectiveness is reported in 2011 US dollars (USD) and is calculated from reported results by first converting the study currency to USD using the Federal Reserve annual exchange rate[47] for the study's currency year and then inflated to 2011 values using the medical care component of the Consumer Price Index.[48]

Finally, up to three additional quality measures are included for each of these studies. The Tufts CEA Registry[49] quality score is recorded when it was available (note it is only available for cost-utility analyses, CUAs). A Jadad score[50] with minor modifications (the two possible points for blinding were replaced with one point for use of a blinded assessor)[51] was calculated for the economic evaluations that included a randomized trial. The percent of the applicable items from the 35-item *BMJ* checklist which were met by each article is also reported.[41]

Results

As shown in Figure 1, the database search identified 270 published economic evaluations. An additional 68 articles were added through the bibliography and expert-supplied list search for a total of 338 economic evaluations of CIM. Of these, 204 (60%) were published from 2001 through 2010 (114 full and 90 partial economic evaluations). Of the recent full economic evaluations almost all (103, 90%) examined the effect of one CIM therapy and most of the balance (10, 9%) examined the effect of two or more CIM therapies provided by the same practitioner. Only one looked at the effect of multiple CIM therapies provided by different CIM providers.[52] CIM was generally evaluated as an adjunct to usual care.

As shown in Table 2, the 204 economic evaluations published in the past 10 years are spread across a wide range of CIM therapies applied to a number of different study populations. The biggest concentration of full economic evaluations (19 in number) pertained to the use of NCCAM's definition of manipulative and body-based practices (e.g., chiropractic, osteopathic manipulation, massage, etc.) for the treatment of back pain.[53-72] However, even this subgroup is

fairly heterogeneous in terms of the therapy (or therapies) tested and/or the type of back pain treated. Eight of these comparisons involved chiropractic care for back pain; one for chronic,[53] one for acute,[57]and six for either type.[59 60 63 64 67 68] Five evaluated spinal manipulation and manual therapy provided by physiotherapists for chronic back pain (one),[65] acute back pain (two),[58 69] or either (two).[56 68] Four involved osteopathic manipulation; one for chronic[71] and one for subacute back pain,[72] and two for musculoskeletal conditions including back pain.[66 68] Three evaluated massage; two for chronic[55 62] and one for acute back pain.[57] The last two studies evaluated a musculoskeletal physician (treatment "with a combination of manual therapy, injections, acupuncture, and other pain management techniques") for orthopedic referrals;[54] and a Finnish folk medicine practice called "bone setting" for the treatment of patients with chronic back pain.[61]

Table 3 shows the results of the application of the 35-item *BMJ* checklist to the full economic evaluations published 2001-2010.[41] On average, the number of applicable items met by each article stayed fairly constant during this period. However, the application of two key items (i.e., the proper use of discounting and the inclusion of sensitivity analysis) and the disclosure of funding sources improved significantly, and reporting of the study time horizon worsened significantly. As expected, the average overall and individual-item percentages were higher for the higher-quality articles (those meeting the five study-quality criteria) and for cost-utility analyses (CUAs) of CIM. It is not surprising that CUA's quality is higher. They generally involve more effort than other cost-effectiveness analyses and are required or recommended by various national guidelines.[73-76] Nevertheless, it seems as though the quality of CUAs of CIM is generally comparable to, or slightly better than, that seen in CUAs across all medicine, at least in

terms of the Tufts quality score, disclosure of funding sources, and the five items where comparable data are available.[77 78]

The number of full evaluations meeting each of the five study-quality criteria are: comparison to usual care 97 (85%), all costs from a recognized perspective 96 (84%), health outcomes from a randomized or matched-control trial 86 (75%), patient-specific data on both costs and outcomes 105 (92%), and sensitivity analyses 37 (32%). Sixty-two (54%) of full evaluations met the first four of these and 31 (27%) met all five. A summary of the results of these 31 higher-quality articles (covering 28 different studies) is shown in Table 4.[54 60 62 68 71 79-104] Twenty-two of these articles (19 of the studies) reported resource use (trials) or model parameters (models) separate from unit prices—a minimum measure of study transferability. For those studies which included a randomized trial, the modified Jadad scores ranged from 2 to 4 on a scale from 0 to 4. The Tufts CEA Registry quality scores for the studies containing a CUA ranged from 4 to 6.5 on a scale from 1 to 7. The percent of the applicable items on the BMJ checklist met by these studies ranged from 66 to 97 percent.

Of the 56 comparisons made in these studies, 16 (29%) are cost-saving—i.e., the added CIM therapy had better health outcomes and lower costs than usual care alone. Of the 28 cost-utility comparisons, one (massage for low back pain[62]) was dominated—i.e., had worse health outcomes and higher costs than usual care. Five (18%) are cost saving, 5 (18%) have incremental cost-effectiveness ratios (ICERs) between $0 and $10,000 per quality-adjusted life-year (QALY), and 89 percent had ICERs less than $50,000/QALY, a threshold often considered to represent the upper limit of society's value for a QALY.[105] The average percent of applicable

BMJ checklist items met by each study was slightly lower for those studies with at least one cost-saving comparison (85% versus 88%), but the difference was not statistically significant (t-test=0.75, p-value=.460).

Discussion

This comprehensive systematic review identified 338 economic evaluations of complementary and integrative medicine (CIM); 204 of which were published recently (2001-2010) covering a wide range of CIM therapies for a variety of populations. Although most patients who use CIM use more than one modality[35] and despite the attention given to integrative medicine (coordinated access to conventional medicine and CIM),[106] this systematic review found only one study that examined the effects of use of multiple CIM practitioners.[52] In general, the quality of the recent full economic evaluations has held constant and is in line with what is seen in economic evaluations in conventional medicine. Details of the 31 recent higher-quality full economic evaluations indicate potential cost-effectiveness and cost savings across a variety of CIM therapies applied to different conditions. Due to the non-generalizable nature of economic evaluations, the cost estimates shown are specific to their study settings.[40] However, 22 articles provided at least the minimum information for study transferability. Therefore, their results could be adapted via modeling to determine the economic impact of these interventions in other settings.

The strengths of this study are the comprehensive search strategy, which revealed a substantial number of published economic evaluations of CIM, the use of two reviewers, and the use of

multiple measures of study quality. Higher-quality studies were identified and highlighted for policy makers using a simple objective list of quality criteria, which reduced the potential for bias. The weaknesses of this study are similar to those of the other systematic reviews. The reviewers were not blinded to journals and article authors, which may have influenced results. Also, some aspects of what makes a quality economic evaluation could not be judged from what was reported. For example, ideally, pragmatic trials enroll patients typical of normal caseload in typical settings with typically-trained and experienced practitioners following them under routine conditions.[37p251] Judgments as to whether these criteria were met were not always possible from the reports, and were beyond the scope of this review. Finally, publication bias was not assessed. However, since the major goal of this study was to establish the extent of the published literature on this topic and to highlight the results of the higher-quality studies, it is not clear that publication bias is relevant here.

The number of economic evaluations of CIM found and reviewed by this study far exceeds the numbers found in previous studies.[11 19-21 23] This study found a total of 338 economic evaluations of CIM published between and including 1979 and 2010; 211 of these were full economic evaluations. White and Ernst [19] identified 34 economic evaluations of CAM published 1987-1999; 11 of which were full economic evaluations. Between 1999 and October 2004, Herman et al[20] identified 56 economic evaluations of CAM (39 full evaluations). Between 1994 and May 2004 Hulme and Long[21] identified 19 full economic evaluations of CAM, and over a similar period (1995-2007) Doran et al[23] found 43 economic evaluations (15 full evaluations). Maxion-Bergemann et al[11] identified five (one full) economic evaluations over an unspecified search period. The large number of economic evaluations found in this study reflects the facts that: 1)

all evaluations from previous reviews were included; 2) a number of studies have been published since the last search dates of prior reviews; and 3) a more extensive search strategy was used. It should be noted that 20 percent of the articles (68 of 338) in this review were identified through bibliography searches and from expert lists. Therefore, even the application of a long list of search terms to multiple databases does not guarantee that all CIM studies will be identified. However, there is some evidence that the indexing of these articles in medical databases is improving; studies from bibliographies and expert lists made up 32 percent of found articles published 2000 and before, but only 12 percent more recent articles.

There are several implications of this study for policy makers, clinicians, and future researchers. First, there is a large and growing literature of quality economic evaluations in CIM. However, although indexing is improving in databases, finding these studies can require going beyond simple CIM-related search terms. Second, the results of the higher-quality studies indicate a number of highly cost-effective, and even cost saving, CIM therapies. Almost 30 percent of the 56 cost-effectiveness, cost-utility and cost-benefit comparisons shown in Table 4 (18 percent of the CUA comparisons) were cost saving. Compare this to 9 percent of 1433 CUA comparisons found to be cost saving in a large review of economic evaluations across all medicine.[107] Third, by meeting the five study quality criteria, the studies shown in Table 4 can each be considered a reasonable indicator of the health and economic impacts of the CIM therapy studied, at least in that population and setting. These studies, especially those showing cost savings, should be considered further for applicability in other settings. This requires the study to be transferable.[39] Fortunately, 19 of the 28 studies (22 of the 31 articles) met our measure of study transferability—resource use or model parameters, and unit costs were reported separately.

Given the substantial number of economic evaluations of CIM found in this comprehensive review, even though it can always be said that more studies are needed, what is actually needed are better quality studies—both in terms of better study quality (to increase the validity of the results for its targeted population and setting) and better transferability (to increase the usefulness of these results to other decision makers in other settings). Therefore, the following recommendations are made.

1. That all studies measuring the effectiveness of CIM at least consider also measuring input costs and economic outcomes.
2. That at least one arm of the study be some version of commonly available ("usual") care, and that usual care and all interventions studied be described in sufficient detail that decision makers in other settings can determine what was done and whether the study's usual care comparator is applicable in their setting.
3. That consideration be given to how CIM is typically used (e.g., multiple CIM therapies) or can be used (e.g., coordinated integrative care models) when designing studies.
4. That the study population be a well-defined sample of typical patients seen for the condition of interest, and described in sufficient detail so that decision makers in other settings can determine comparability to their population.
5. That all costs from the societal perspective be included where possible. Since this perspective contains all costs, those interested in results from other perspectives will be able to extract the costs they need.

6. That changes in resource use be reported separately from unit costs in economic evaluations alongside clinical trials and that model parameters and unit costs be clearly reported in decision-analytic modeling studies.
7. That all economic evaluations contain sensitivity analyses to increase the reliability of results.
8. That more consideration be given to modeling as a method to estimate economic outcomes for existing effectiveness trial results, and to generalize existing quality economic evaluation results to other jurisdictions.

Licensure

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: funds from the Bernard Osher Foundation

supported a portion of DME's time on the submitted work; no other support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

PMH conceived of the idea for the paper, designed the search strategy, reviewed the references found, extracted the data from each included article, and is the guarantor for this study. In parallel, BLP also reviewed the references found, extracted data from included articles, and worked with PMH to resolve any discrepancies between reviewers. CMW provided practical insight and an international perspective to the design of the paper and interpretation of results. DME participated in the early design of the study, including the data extraction plan, inclusion/exclusion criteria, and the interpretation of results. All authors contributed to the drafting and editing of the manuscript.

Ethical approval

No ethical approval was required as this is a review of published work.

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Data sharing statement

The full list of found articles is available in a Word document from the corresponding author.

PRISMA statement

The manuscript was prepared following the PRISMA guidelines. A PRISMA checklist is included as a supplemental file.

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Table 1. Types of full economic evaluations

	Cost-benefit analysis (CBA)	Cost-effectiveness analysis (CEA)	Cost-utility analysis (CUA) (a special case of CEA)
Unit of health outcome	Monetary units (e.g., US dollars)	Natural units (e.g., life-years gained)	Units of overall impact on length and quality of life (e.g., quality-adjusted life-years, QALY)
Results	Net benefits $(B_1-B_2) - (C_1-C_2-S_1+S_2)$	Cost-effectiveness ratio* $(C_1-C_2-S_1+S_2)/(E_1-E_2)$	Cost-utility ratio* $(C_1-C_2-S_1+S_2)/(QALY_1-QALY_2)$

* Ratios are calculated when both the costs and the effects (health improvements) of one therapy alternative are higher than those of another. When the costs are lower and the effects are better for one therapy, it is said to dominate the alternative (and the alternative is said to be dominated) and no ratio is presented. B1 = monetary value of health outcomes of alternative 1; B2 = monetary value of health outcomes of alternative 2; C1 = total input costs of alternative 1; C2 = total input costs of alternative 2; S_1 = total cost savings (economic outcomes) for alternative 1; S_2 = total cost savings (economic outcomes) for alternative 2; E1 = health effects of alternative 1; E2 = health effects of alternative 2; QALY1 = quality-adjusted life-years of alternative 1; QALY2 = quality-adjusted life-years of alternative 2.

Table 2. Types of individual complementary and integrative medicine (CIM) therapies studied for various conditions and in various populations: 2001-2010 (reported as the ratio of the total number of economic evaluations to the number of full economic evaluations)

	Manipulative and body-based practices	Acupuncture	Natural Products	Other Mind-body medicine	Homeopathy	CIM in general	Other CIM therapies*	TOTALS†
Back pain	28:19	11:10	2:2	-	1:1	3:0	2:2	42:29
Rheumatic disorders	9:5	6:4	6:6	2:2	-	1:0	4:3	27:19
Mixed populations	4:1	6:1	2:1	3:1	9:5	2:1	3:2	24:9
Cardiovascular disease and diabetes	-	1:0	8:6	6:4	1:1	-	3:1	18:12
Infection (various)	-	-	6:4	-	7:4	-	-	13:8
Surgery	1:1	2:2	4:3	5:4	-	-	-	12:10
Members of insurance plans	3:0	2:0	-	-	1:0	7:0	-	12:0
Mental disorders	-	2:2	-	5:3	1:1	1:0	2:0	11:6

(various)								
Older populations	-	-	6:3	2:0	-	-	3:1	11:4
Headaches	1:0	3:3	-	4:3	1:1	-	-	9:7
Children (various conditions)	1:0	-	-	-	6:4	1:0	1:0	9:4
Cancer	2:1	2:1	1:1	2:2	-	2:0	-	8:4
Pregnancy and women's health	-	5:5	1:0	1:0	-	-	-	7:5
Allergies	-	1:1	-	-	3:1	-	1:1	5:3
Other conditions‡	1:1	1:1	3:3	5:4	2:1	2:0	6:2	19:11
TOTALS†	45:25	41:29	38:28	27:16	24:13	18:1	25:12	204:114

* Other CIM therapies included aromatherapy, healing touch, Tai Chi, Alexander technique, spa therapy, music therapy, electrodermal screening, clinical holistic medicine, naturopathic medicine, anthroposophic medicine, water-only fasting, Ornish Program for Reversing Heart Disease, use of a corset, and use of a traditional mental health practitioner.

† Totals across (down) columns will not add to numbers in the totals column (row) due to individual studies addressing more than one CIM therapy (patients in more than one group).

‡ Other conditions studied included patients with multiple chemical sensitivities, respiratory disease, pharyngeal dysphagia, dyspepsia, functional bowel disorders, other functional disorders, venous leg ulcers, major burns, and constipation; patients who rated themselves as physically ill or having low quality of life; patients in home hospice or with home nursing; long-term care workers; and prisoners.

Table 3. Comparison of various quality measures between economic evaluations of complementary and integrative medicine (CIM) and conventional medicine

	Economic evaluations of CIM					CUAs across all medicine*	
	All Full n=114	2001-2005 n=59	2006-2010 n=55	Higher quality n=31	CUAs n=27	1998-2001 n=300	2002-2005 n=637
Average % met of applicable items on *BMJ* checklist	72%	71%	73%	87%	89%		
Presented the study perspective clearly	61%	58%	64%	87%	93%§	74%	83%§
Presented the study time horizon	96%	98%‡	93%‡	100%	100%‡	75%	87%‡
Conducted and reported sensitivity analysis	32%	22%§	44%§	100%	93%§	93%	84%§
Discounted costs and health effects, where appropriate#	60%	25%‡	76%‡	94%	100%‡	85%	84%‡
Stated year of currency for resource costs	59%	54%	60%	77%	78%§	83%	85%§
Separate reporting of resource use (trials), parameters (models), and unit costs (for transferability)	52%	51%	53%	71%	70%		
Disclosed funding sources	72%	58%‡	76%‡	84%	93%‡	65%†‡	
Industry sponsored	10%	12%	11%	10%	7%	18%†	
Average Tufts quality score (CUAs only)					4.75¶	4.25†¶	

* Data from Table 3 in Neumann PJ. Costing and perspective in published cost-effectiveness analysis. *Medical Care.* 2009;47(Suppl 1):S28-S32.

† Data from Table 3 in Neumann PJ, Greenberg D, Olchanski NV, Stone PW, Rosen AB.Growth and quality of the cost-utility literature, 1976-2001. *Value in Health* 2005;8(1):3-9. Industry sponsored was calculated as a percent all studies 1976-2001.

‡χ^2 test p-value<.001; §χ^2 test p-value<.01; ¶t-test p-value=.002; Comparisons were made between CIM economic evaluations published 2001-2005 and those published 2006-2010, and between CUAs of CIM 2001-2010 and CUAs of all medicine 2002-2005.

Denominators for the percentages reported in this row are the number of studies which evaluated impacts past one year in either the base case or in sensitivity analyses. For the first five columns the denominators are 25, 8, 17, 16, and 11, respectively. This information was not available for the last two columns.

CUA = cost-utility analysis

Table 4. Summary of results of complementary and integrative medicine (CIM) economic evaluations that met five study quality criteria (31 articles representing 28 studies)

	CIM Therapy Compared to Usual Care Alone*	Treatment duration / Study duration	Patient Population	Primary Outcome(s)	Setting (information often limited by what was reported)	Sample Size	Study design and quality scores†	Resource Use (Trials), Parameters (Models), and Unit Costs (Both) Reported Separately?	Form and Perspective of Economic Evaluation	Incremental Cost-Effectiveness Ratio (2011 USD)‡
Acupuncture studies										
Brown et al (2001) *Health Bull*	Adjunctive acupuncture, manual therapy, injections and other pain management	Up to 1 year / 1 year	Patients referred for an orthopedic outpatient consultation who were classified as unlikely to require surgery	Clinical: SF-36 and, if appropriate, Aberdeen Low Back Pain Scale or Edinburgh Knee Function Scale; Economic: EQ5D	Individualized care from one "physical medicine" physician in a hospital outpatient clinic in Scotland	829	R (2) 81% BMJ	Yes	CEA – H CUA – H	Cost saving Cost saving

van den Berg et al. (2010) *Complement Ther Med*	Adjunctive breech version acumoxa	2 visits / From 33 weeks to delivery	Pregnant women with breech presentation at 33 weeks	Economic: percent of breech presentations at delivery – two "main analyses" – with and without the option of external cephalic versions	2 instructional visits to an acupuncturist followed by daily home self-care Netherlands	NA	M 81% BMJ	Yes	CEA – P CEA – P	Cost savings Cost savings
Ratcliffe et al. (2006) *BMJ* and Thomas et al. (2005) *Health Tech Assess*	Adjunctive acupuncture	3 months / 2 years	Patients with low back pain	Clinical: Bodily pain fm SF-36; Economic: QALYs fm SF-6D	Up to 10 treatments from a TCM-trained acupuncturist in acupuncture clinic in UK	239	R (3) Tufts 5 94%/94% BMJ	Yes	CUA – S CUA – P	Cost saving $8755/QALY

Kim et al. (2010) *BMC CAM*	Adjunctive acupuncture	10 treatments in 3 month cycles / 5 years	60-year-old females with 1st time acute low back pain	Clinical: Roland-Morris Disability, Symptom bothersomeness; Economic: QALYs fm literature	Hospital-based licensed Oriental medical doctors in South Korea	NA	M Tufts 4.5 94% BMJ	Yes	CUA – S	$3086/QALY
Witt et al. (2008) *Am J Obs Gyn*	Adjunctive acupuncture	3 months / 6 months	Patients with dysmenorrhea	Clinical: Pain Intensity VAS; Economic: QALYs fm SF-6D	Up to 15 sessions with a physician trained in acupuncture (A-diploma) in Germany	201	R (3) Tufts 5.5 77% BMJ	No	CUA – S	$4708/QALY§

Witt et al. (2006) *Am J Epidemiol*	Adjunctive acupuncture	3 months / 6 months	Patients with chronic low back pain	Clinical: Hannover Functional Ability Questionnaire; Economic: QALYs fm SF-6D	Up to 15 sessions with a physician trained in acupuncture (A-diploma) in Germany	2,518	R (3) Tufts 4.5 73% BMJ	No	CUA – S	$16,230/QALY§
Witt et al. (2008) *Cephalalgia*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with headache	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	3,182	R (2) Tufts 5.5 88% BMJ	No	CUA – S	$18,225/QALY§
Willich et al. (2006) *Pain*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with chronic neck pain	Clinical: Neck Pain and Disability Scale; Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	3,451	R (2) Tufts 5 88% BMJ	No	CUA – S	$19,226/QALY§

Wonderling et al. (2004) *BMJ* and Vickers et al. (2004) *Health Tech Assess*	Adjunctive acupuncture	3 months / 1 year	Patients with chronic headache	Clinical: headache severity score; Economic: QALYs fm SF-6D	Acupuncture-trained physio-therapists in own clinics in UK	401	R (3) Tufts 5 97% / 93% BMJ	Yes	CUA – S CUA – P	$19,785/QALY $21,074/QALY
Reinhold et al. (2008) *Eur J Health Econ*	Adjunctive acupuncture	3 months / 3 months	Patients with chronic hip or knee osteoarthritis	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma), Germany	489	R (3) Tufts 4 87% BMJ	No	CUA – S	$27,900/QALY§
Witt et al. (2009) *Am J Epidemiol*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with allergic rhinitis	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	981	R (3) Tufts 4 94% BMJ	No	CUA – S	$28,137/QALY§
Manipulative and body-based practices – See also Brown et al, 2001, above.										

Korthals-de Bos et al. (2003) *BMJ*	Manual therapy	6 weeks / 1 year	Patients with neck pain	Clinical: Perceived recovery, pain VAS, and Neck Disability Index; Economic: All clinical plus QALYs fm EQ-5D	Up to 6 weekly 45 min sessions with a physiotherapist who is also a registered manual therapist in the Netherlands	183	R (3) Tufts 6.5 83% BMJ	Yes	CEA – S CEA – S CEA – S CUA – S	Cost saving Cost saving Cost saving Cost saving
Williams et al. (2004) *Fam Pract*	Adjunctive osteopathic spinal manipulation	2 months / 6 months	Patients with subacute (2-12 week) back pain	Clinical: Extended Aberdeen Spine Pain Scale; Economic: QALYs fm EQ-5D	3 or 4 sessions with a general practitioner who is a registered osteopath at own clinic in UK	187	R (3) Tufts 5 89% BMJ	Yes	CUA – P	$8730/QALY

UK BEAM Trial Team. (2004) *BMJ*	Adjunctive spinal manipulation and exercise	3 months / 1 year	Patients with low back pain	Economic: QALYs fm EQ-5D	8 sessions with a chiropractor, osteopath, or physiotherapist at a private or NHS site in UK	1,287	R (3) Tufts 6 93% BMJ	Yes	CUA – P	$8425/QALY
	Adjunctive spinal manipulation								CUA – P	$10,642/QALY
Hollinghurst et al. (2008) *BMJ* [1]Compared to usual care plus exercise	Alexander technique	6 lessons / 1 year	Patients with chronic or recurrent non-specific back pain	Clinical: Roland-Morris Disability Questionnaire (RMDQ); Economic: Above plus QALYs fm EQ-5D	Alexander technique teachers and massage therapists at own locations in UK	579	R (3) Tufts 5.5 97% BMJ	Yes	CUA – P CEA – P	$13,300/QALY $255/RMDQ pt
	Alexander technique plus exercise[1]	6 lessons / 1 year							CUA – P CEA – P	$12,022/QALY $144/RMDQ pt
	Massage	6 sessions / 1 year							CUA – P CEA – P	Dominated $1010/RMDQ pt
	Massage plus exercise[1]	6 sessions / 1 year							CUA – P CEA – P	$11,959/QALY $354/RMDQ pt
Haas et al. (2005) *J Manip Physiol Ther*	Treatment in a chiropractic clinic	Un-specified /	Patients with acute low back pain	Clinical and Economic: pain severity 100mm	Doctors of Chiropractic in	1,943	MC 66% BMJ	No	CEA – P	$21/pain mm

		1 year	Patients with chronic low back pain	VAS and Revised Oswestry Disability Questionnaire	own clinics in Oregon, USA	837			CEA – P	$0.73/pain mm
Natural products										
Braga, et al. (2005) *Nutrition*	Adjunctive pre-operative arginine and omega 3 fatty acid supplementation	5 days / 5 days plus hospital stay	Patients with gastrointestinal cancer undergoing surgery	Economic: percent of patients without complications	12.5g arginine, 3.3g omega 3 fatty acids, and 1.2g RNA in liquid daily taken orally for 5 days before surgery, Italy	204	R (3) 88% BMJ	No	CEA – H	Cost saving
Stevenson et al. (2010) *Med Decis Making* and Stevenson et al. (2009) *Health Technol Assess*	Vitamin K1	10 years / 10 years	Postmenopausal women with osteoporosis/ osteopenia	Clinical: Osteoporotic fracture Economic: QALYs fm the literature	10mg/d of vitamin K1 daily, UK	NA	M Tufts 4.5 81% / 84% BMJ	Yes	CUA – P	Cost saving

Trevithick et al. (2006) *J Orthomol Med*	Adjunctive antioxidants (vitamins C and E and beta-carotene)	25 years / 25 years	Cohort of Ontario residents aged 50-54 (prevention of cataracts)	Clinical: cataract formation	750mg/d vitamin C, 600mg/d vitamin E, & 18mg/d beta-carotene daily, Canada	NA	M 79% BMJ	Yes	CEA – P	Cost saving
Schmier et al. (2006) *Manag Care*	Adjunctive omega 3 fatty acid supplementation	42 months / 42 months	Males with a history of a heart attack	Economic: fatal MIs and cardiovascular deaths	"fish oil pills," USA	NA	M 77% BMJ	Yes	CEA – S CEA – P	Cost saving $11,903/fatal MI avoided

Lamotte et al. (2006) *Pharmacoecon*	Adjunctive omega-3 polyunsaturated fatty acids	3.5 years / Lifetime	Patients after an acute myocardial infarction	Economic: life-years saved	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, Australia, Belgium, Canada, Germany and Poland	NA	M 89% BMJ	Yes	CEA –P CEA –P CEA –P CEA –P CEA –P	$5413/LYG Australia $8184/LYG Belgium $4476/LYG Canada $6750/LYG Germany $7747/LYG Poland
Quilici et al. (2006) *Int J Clin Pract*	Adjunctive omega-3 polyunsaturated fatty acids	4 years / Lifetime	Patients after an acute myocardial infarction	Economic: life-years gained (LYG), QALYs fm the literature, deaths avoided	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, UK	NA	M Tufts 5 93% BMJ	Yes	CEA –P CUA – P	$28,420/LYG $35,940/QALY

Franzosi et al. (2001) *Pharmacoecon*	Adjunctive omega-3 poly-unsaturated fatty acids	3.5 years / 3.5 years	Patients with recent myocardial infarction	Clinical: death and non-fatal MI or stroke; Economic: life-years gained (LYG)	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, Italy	5,664	R (4) 85% BMJ	No	CEA – P	$41,867/LYG
Black et al. (2009) *Health Technol Assess*	Adjunctive glucosamine sulfate	22.6 years / 22.6 years	Patients with osteoarthritis of the knee	Clinical: Pain, function, joint space loss Economic: QALYs fm the literature	Glucosamine sulfate powder 1500mg daily in oral solution, UK	NA	M 84% BMJ	Yes	CUA-P	$59,053/QALY
Other complementary and integrative medicine therapies										
Wilson and Datta. (2001) *J Clin Outcomes Manag*	Adjunctive yang-style tai chi	1 year / 1 year	Nursing home residents at average risk for a fall	Economic: hip fractures avoided	2 classes/week monitored by a certified tai chi instructor & an assistant, USA	NA	M 96% BMJ	Yes	CEA – P	Cost saving

Herman et al. (2008) *Altern Ther Health Med*	Adjunctive naturopathic care including acupuncture, relaxation exercises, dietary and exercise advice	3 months / 6 months	Patients with chronic low back pain	Clinical: Oswestry Disability Questionnaire; Economic: QALYs fm SF-6D	Twice weekly visits to licensed naturopathic doctors also trained in acupuncture in a worksite clinic in Canada	70	R (3) Tufts 5 96% BMJ	Yes	CUA – S CEA – E CBA – E	Cost saving $191/absentee day avoided Cost saving

Van Tubergen et al. (2002) *Arthritis Rheum*	Combined spa-exercise therapy	3 weeks / 40 weeks	Patients with ankylosing spondylitis	Clinical: Bath Ankylosing Spondylitis Functional Index (BASFI 10pts), pain VAS, well-being VAS, and morning stiffness in minutes; Economic: Above plus QALYs fm EQ-5D	3-week stay at one of two spa-resorts with therapy provided by trained physio-therapists, Netherlands	120	R (3) Tufts 4.5 90% BMJ	Yes	CEA – S CEA – S CUA – S CUA – S	$2159/BASFI pt (spa in Austria) $4215/BASFI pt (spa in the Netherlands) $12,703/QALY (spa in Austria) $31,609/QALY (spa in the Netherlands)
Zijlstra et al. (2007) *Rheum*	Adjunctive spa therapy	2.5 weeks / 1 year	Patients with fibromyalgia	Economic: QALYs fm VAS and SF-6D	18-day stay at a spa in Tunisia with a variety of treatments, Netherlands	128	R (3) Tufts 4 97% BMJ	Yes	CUA – S CUA – S	$46,443/QALY (VAS) $92,886/QALY (SF-6D)

* The use of the term "adjunctive" in this column indicates CAM therapies used in addition to usual care for that condition unless otherwise indicated.

† Study design: R = randomized, MC = matched controls and/or results statistically adjusted for baseline differences, M=modeling study. A modified Jadad score (maximum score = 4) is provided if the study was randomized. If the study was a CUA and a quality score was available from the Tufts Medical Center Institute for Clinical Research and Health Policy Studies CEA Registry (https://research.tufts-

nemc.org/cear/Default.aspx), it is reported. Quality scores range from 1 to 7 with 7 representing the highest quality. The last number is the percent of the applicable items on the BMJ 35-item quality checklist that this study met. If a study had more than one publication, both percentages were reported. The BMJ checklist is found in Drummond MF, Jefferson TO, BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275-283.

‡ The costs reported in each study were first converted to US dollars (USD) using the Federal Reserve annual exchange rate (http://www.federalreserve.gov/releases/g5a/20090102/, accessed Jan 30,2012) for the study's currency year and then inflated to 2011 values using the medical care component of the Consumer Price Index (http://www.bls.gov/cpi/cpi_dr.htm#2007, accessed Jan 30, 2012). In comparisons labeled as cost saving the CIM therapy both improved health and lowered costs compared to usual care. In the comparison labeled dominated the CIM therapy had worse health outcomes and higher costs than usual care.

§ These studies did not report a currency year so it was estimated as being one year prior to publication.

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CBA=cost-benefit analysis.

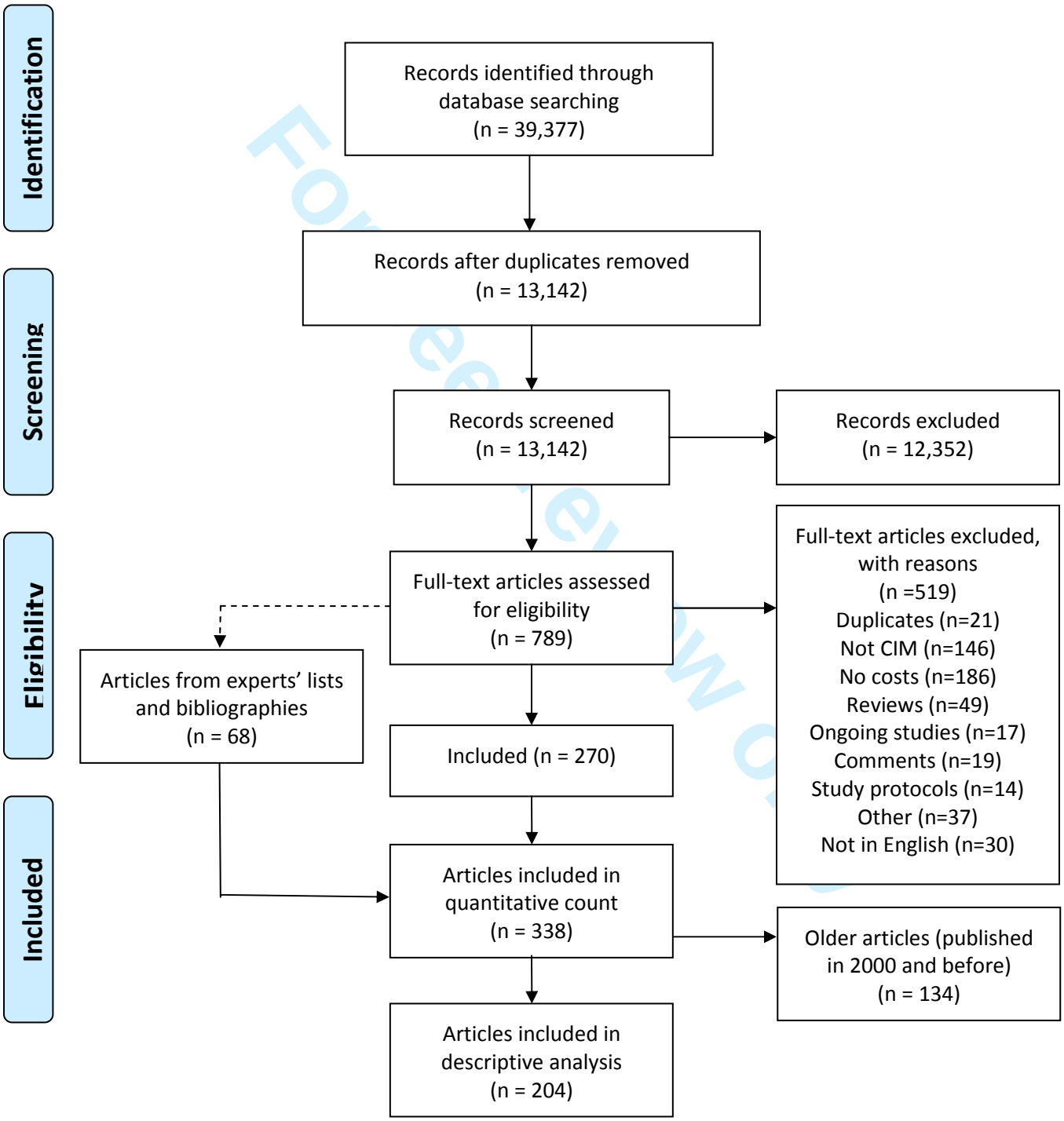
P = Payer perspective; S = Societal perspective; E = Employer perspective; H = Hospital perspective

QALY = quality-adjusted life-year; VAS = visual analog scale

Figure legends

Figure 1. The flow of records and articles through the systematic review

PRISMA 2009 Flow Diagram



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6-7
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	8
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Does not exist
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8-10
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	8-9
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	9-10
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	10
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	10-12
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA, see p17
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	13

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Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA see p17
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 2 & 4, p15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 4
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
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Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Are Complementary Therapies and Integrative Care Cost-Effective? A Systematic Review of Economic Evaluations

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Are Complementary Therapies and Integrative Care Cost-Effective? A Systematic Review of Economic Evaluations

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Economics of complementary and integrative medicine

Abstract

Objective. A comprehensive systematic review of economic evaluations of CIM to establish the value of these therapies to health reform efforts.

Data sources. PubMed, CINAHL, AMED, PsychInfo, Web of Science, and EMBASE were searched from inception through 2010. In addition, bibliographies of found articles and reviews were searched, and key researchers contacted.

Eligibility criteria for selecting studies. Studies of CIM were identified using criteria based on those of the Cochrane CAM group. All studies of CIM reporting economic outcomes were included.

Study appraisal methods. All recent (and likely most cost-relevant) full economic evaluations published 2001-2010 were subjected to several measures of quality. Detailed results of higher-quality studies are reported.

Results. A total of 338 economic evaluations of CIM were identified, of which 204, covering a wide variety of CIM for different populations, were published 2001-2010. 114 of these were full economic evaluations. 90 percent of these articles covered studies of single CIM therapies and only one compared usual care to usual care plus access to multiple licensed CIM practitioners. Of the recent full evaluations, 31 (27%) met five study-quality criteria, and 22 of these also met the minimum criterion for study transferability ("generalizability"). Of the 56 comparisons made in the higher-quality studies, 16 (29%) show a health improvement with cost savings for the CIM therapy versus usual care. Study quality of the cost-utility analyses (CUAs) of CIM was generally comparable to that seen in CUAs across all medicine according to several measures,

and the quality of the cost-saving studies was slightly, but not significantly, lower than those showing cost increases (85% versus 88%, p=.460).

Conclusions. This comprehensive review identified many CIM economic evaluations missed by previous reviews and emerging evidence of cost-effectiveness and possible cost savings in at least a few clinical populations. Recommendations are made for future studies.

Article summary

Article focus

- Given the limited nature of previous systematic reviews, what is the extent of evidence on the economic impacts of complementary and integrative medicine (CIM)?
- What are the range of therapies and populations studied, and the quality of published economic evaluations of CIM?
- What are the results of the higher-quality, more recent (and likely most cost-relevant) economic evaluations of CIM?

Key messages

- This study's comprehensive search strategy identified 338 economic evaluations of CIM, including 114 full evaluations published 2001-2010.
- The cost-utility analyses found were of similar or better quality to those published across all medicine.
- The higher-quality studies indicate potential cost-effectiveness, and even cost savings across a number of CIM therapies and populations.

Strengths and limitations of this study

- The strengths of this study are the comprehensive search strategy, the use of two reviewers, the use of multiple measures of study quality, and the identification of higher-quality studies, for which results are reported in detail, via an objective short-list of quality criteria, which reduced the potential for bias.
- The weaknesses of this study are similar to those of the other systematic reviews: reviewers were not blinded to journals and article authors, and some aspects of what makes a quality economic evaluation could not be judged from what was reported.
- Publication bias was not assessed. However, it is not clear whether publication bias is relevant given the purposes of this review.

Introduction

Between 1990 and 2007, four nationally representative surveys demonstrated that a third or more of US adults routinely used complementary and alternative medicine (CAM) therapies to treat their principal medical conditions.[1-4] Total expenditures for CAM therapies were estimated at $14 Billion in 1990,[1] $27 Billion in 1997,[2] and $34 Billion in 2007.[4] The 2007 US National Health Inventory Survey found that out-of-pocket expenditures for CAM therapies accounted for 11 percent of all out-of-pocket health care expenditures by Americans.[4] Similar use numbers are seen in other countries.[5-8] However, despite the popularity of and substantial expenditures on CAM therapies, their cost effectiveness remains ill-defined and controversial.

Economic evaluations allow costs to be included, alongside data on safety and effectiveness, in healthcare policy decisions. As healthcare costs rise, the availability of these economic evaluations becomes increasingly important to the formulation of disease management strategies which are both clinically effective and financially responsible. According to the National Center for Complementary and Alternative Medicine (NCCAM), complementary and alternative medicine (CAM) is "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine."[9] In not being part of conventional medicine, individual complementary therapies and emerging models of integrative medicine (i.e., coordinated access to both conventional and complementary care)—collectively termed complementary and integrative medicine (CIM)—are often excluded in financial mechanisms commonly available for conventional medicine,[2] and are rarely included in the

range of options considered in the formation of healthcare policy. The availability of economic data could improve the consideration and appropriate inclusion of CIM in strategies to lower overall healthcare costs. In addition, economic outcomes are relevant to the licensure and scope of practice of practitioners, industry investment decisions (e.g., the business case for integrative medicine), consumers, and future research efforts (i.e., through identifying decision-critical parameters for additional research[10]).

A number of systematic reviews of economic evaluations of CIM have been published.[11-23] Five of these prior reviews attempted to capture all economic evaluations of CIM therapies across all conditions.[11 19-21 23] However, it is unclear whether all or even the majority of economic evaluations of CIM have been identified by these reviews. The searches are dated; the search strategy in the most recent review only captured articles published through 2007.[23] The databases searched were limited—e.g., only one used CINAHL,[21] and only two others used EMBASE,[19 23] both in addition to Medline and AMED. Finally, these reviews generally used limited search terms to identify CIM studies. All but one only used variations on the terms "complementary" or "alternative" "medicine" or "therapy". Unfortunately, other reviewers have found that these search terms do not capture all CIM studies,[24 25] which may be a reflection of the difficulty in defining what is and is not CIM.[26] The search by Maxion-Bergemann and others[11] also added individual therapies as search terms, but only included homeopathy, phytotherapy, Traditional Chinese Medicine, anthroposophic medicine, and neural therapy. No search included "integrative medicine."

The goal of this paper is to identify, to the extent possible, all published economic evaluations of complementary and integrative medicine (CIM), describe the types of CIM evaluated and the clinical conditions for which they have been evaluated, and identify the more recent (and therefore, most cost-relevant) higher-quality studies and highlight their results for policy makers. We also make recommendations for future economic evaluations of CIM.

Methods

Six electronic databases were searched from their inception through December 2010: PubMed, CINAHL, AMED, PsychInfo, Web of Science, and EMBASE. To be as comprehensive as possible, a combination of 11 medical subject heading (MeSH) and 39 other search terms were used (see Box 1). In addition, bibliographies of found articles and reviews were searched, and key researchers in various areas of CIM were contacted for their lists of known studies. Although non-English language articles were collected, they are not analyzed in this review.

Box 1. Search terms used for the PubMed search: (Complementary Therapies [MeSH], Dietary Supplements [MeSH], Micronutrients [MeSH], Trace Elements [MeSH], Vitamins [MeSH], acupuncture, alternative medicine, ayurvedic medicine, chiropractic, biofeedback, collaborative medicine, complementary and alternative medicine, botanical medicine, complementary medicine, diet, energy medicine, herbal medicine, herbs, homeopathy, hypnosis, integrated medicine, integrative medicine, massage, meditation, mind-body medicine, minerals, naturopathic medicine, naturopathy, nutrients, nutritional supplements, relaxation, spa therapy, traditional Chinese medicine, OR vitamins) AND (Cost-Benefit Analysis [MeSH], Cost Control [MeSH], Cost Savings [MeSH], Costs and Cost Analysis [MeSH], Economics [MeSH],

economics [Subheading], Insurance [MeSH], cost benefit, cost effectiveness, cost identification, cost minimization, cost utility, economic evaluation, insurance claims, managed care, OR technology assessment). Searches in the other five databases used the same text words and (where available) analogous controlled vocabulary terms. Allsearches were restricted to human studies.

Defining a comprehensive search strategy for CIM is challenging.[24 27-29] There have been a number of efforts to develop a concise definition of CAM.[26 30] This review used the one developed by the members of the Cochrane CAM Field[31] and then added the terms "integrative," "integrated," and "collaborative" medicine. The Cochrane CAM definition starts with the NCCAM definition[9] and then refines it by specifically including all therapies "based upon the theories of a medical system outside the Western allopathic medical model" (e.g., traditional Chinese medicine, Reiki), and including others depending on the context and setting of their use. The context of use considers treatment/condition combinations and excludes those "currently considered to be standard treatment," and the setting of use generally includes self-care and therapies delivered by CIM providers, but excludes therapies "delivered exclusively by conventionally-credentialed medical personnel or exclusively within hospital settings." Therefore, therapies such as chemotherapy regimens (e.g., chronotherapy[32]), and therapies requiring surgical implantation (e.g., neuroreflexotherapy[33]) or the placement of a feeding tube[34] were not included even though these therapies appeared in our search. In cases where CIM therapies (e.g., biofeedback or hypnosis) were included as part of a package of care (e.g., with cognitive behavioral therapy), a judgment was made as to whether the CIM portion of the

treatment made up half or more of the overall package of care under study. If so, the package of care was included as CIM. Because more than half of CIM users use multiple CIM therapies,[35] studies of packages of therapies and coordinated care were identified as such.

Articles were categorized as full economic evaluations if they compared both the costs (inputs) and consequences (economic, clinical, and/or humanistic outcomes[36]) of two or more therapeutic alternatives applied to the same patient population.[37, p11] Otherwise, they were considered partial evaluations, e.g., cost-identification or cost-comparison studies.[38] Studies that estimated resource utilization were included as economic evaluations if the utilization data were detailed enough to allow monetary valuation.

Two reviewers (PMH and BLP) evaluated all articles for inclusion and extracted all data. Disagreements were resolved by discussion between the two review authors, or, if needed, by the other co-authors. Because the results of economic evaluations can rapidly lose relevance with time, mainly due to changes in practice patterns and cost structures, data were extracted only from the economic evaluations published 2001 through 2010. Extracted data were entered into an Excel template developed for a previous review.[20] The type(s) of CIM evaluated and the target population were captured for all economic evaluations. Various indicators of study quality were captured for all full economic evaluations, and more detailed data and results were captured only for those full economic evaluations that met five quality criteria.

The quality of an economic evaluation can be judged along two general dimensions: 1) whether the study was a quality measure of outcomes for its target population and location—i.e., whether

it was internally valid; and 2) whether enough information is provided for the study's results to be transferable ("generalizable").[39] Health outcomes are to some extent considered generalizable across settings, however, because resource availability, practice patterns and relative prices can vary greatly, economic outcomes are usually not.[40] Therefore, one goal in economic evaluation is to ensure the *transferability* of study results—i.e., to provide enough study detail so that results can be adapted (usually via modeling) to apply to other settings.[39] The 35-item *BMJ* checklist captures components of both dimensions of quality and was applied to all full economic evaluations.[41] We also chose five quality criteria by which to identify a subset of full economic evaluations to highlight as being of most interest to policy makers. These quality criteria are based on recommendations made by the US Panel on Cost Effectiveness in Health and Medicine [42] and by well-known experts in the field,[37] and focus on the quality of the underlying study (the first type of quality):

- Because cost effectiveness analysis is comparative, to ensure that results are useful to decision makers, one of the alternatives to which the CIM intervention was compared must be some version of commonly available (routine, standard or usual) care.
- The analysis must explicitly or implicitly use (and include all relevant costs from) at least one recognized perspective—e.g., society, third-party payer, hospital, or employer.
- Since "an economic evaluation of a health care programme is only as good as the effectiveness data it is built upon,"[43, p232] health outcomes must be from randomized controlled trials or non-randomized controlled trials using either statistical adjustment or matching to address baseline differences.

- Since having patient-specific data on both costs and outcomes is an advantage for internal validity,[44] resource use must be a measured outcome of the study. Modeling studies utilize the results of other published studies, therefore, are exempt from this criterion.
- Because uncertainty in an economic evaluation comes not just from sample variation, but also from assumptions made,[45] a sensitivity analysis is required.

Because the prices used to value resources are highly location- and setting-specific,[39 46] we also note, for the articles meeting the above criteria, the presence of a study reporting criterion essential for the transferability of study results (usually via modeling):[39 40] separate reporting of unit costs from resource use for economic evaluations alongside trials, or from model parameters (e.g., transition probabilities) for economic evaluations using models.

Other data extracted for the economic evaluations which meet the five study-quality criteria are: treatment and study duration, primary clinical and economic outcome measures, the setting in which treatment took place, study design and sample size, the type (see Table 1) and perspective (i.e., the point of view used to define costs) of the economic analysis, and incremental cost-effectiveness of the CIM alternative compared to usual care. Incremental cost-effectiveness is reported in 2011 US dollars (USD) and is calculated from reported results by first converting the study currency to USD using the Federal Reserve annual exchange rate[47] for the study's currency year and then inflated to 2011 values using the medical care component of the Consumer Price Index.[48]

Finally, up to three additional quality measures are included for each of these studies. The Tufts CEA Registry[49] quality score is recorded when it was available (note it is only available for cost-utility analyses, CUAs). A Jadad score[50] with minor modifications (the two possible points for blinding were replaced with one point for use of a blinded assessor)[51] was calculated for the economic evaluations that included a randomized trial. The percent of the applicable items from the 35-item *BMJ* checklist which were met by each article is also reported.[41]

Results

As shown in Figure 1, the database search identified 270 published economic evaluations. An additional 68 articles were added through the bibliography and expert-supplied list search for a total of 338 economic evaluations of CIM. Of these, 204 (60%) were published from 2001 through 2010 (114 full and 90 partial economic evaluations). Of the recent full economic evaluations almost all (103, 90%) examined the effect of one CIM therapy and most of the balance (10, 9%) examined the effect of two or more CIM therapies provided by the same practitioner. Only one looked at the effect of multiple CIM therapies provided by different CIM providers.[52] CIM was generally evaluated as an adjunct to usual care.

As shown in Table 2, the 204 economic evaluations published in the past 10 years are spread across a wide range of CIM therapies applied to a number of different study populations. The biggest concentration of full economic evaluations (19 in number) pertained to the use of NCCAM's definition of manipulative and body-based practices (e.g., chiropractic, osteopathic manipulation, massage, etc.) for the treatment of back pain.[53-72] However, even this subgroup is

fairly heterogeneous in terms of the therapy (or therapies) tested and/or the type of back pain treated. Eight of these comparisons involved chiropractic care for back pain; one for chronic,[53] one for acute,[57]and six for either type.[59 60 63 64 67 68] Five evaluated spinal manipulation and manual therapy provided by physiotherapists for chronic back pain (one),[65] acute back pain (two),[58 69] or either (two).[56 68] Four involved osteopathic manipulation; one for chronic[71] and one for subacute back pain,[72] and two for musculoskeletal conditions including back pain.[66 68] Three evaluated massage; two for chronic[55 62] and one for acute back pain.[57] The last two studies evaluated a musculoskeletal physician (treatment "with a combination of manual therapy, injections, acupuncture, and other pain management techniques") for orthopedic referrals;[54] and a Finnish folk medicine practice called "bone setting" for the treatment of patients with chronic back pain.[61]

Table 3 shows the results of the application of the 35-item *BMJ* checklist to the full economic evaluations published 2001-2010.[41] On average, the number of applicable items met by each article stayed fairly constant during this period. However, the application of two key items (i.e., the proper use of discounting and the inclusion of sensitivity analysis) and the disclosure of funding sources improved significantly, and reporting of the study time horizon worsened significantly. As expected, the average overall and individual-item percentages were higher for the higher-quality articles (those meeting the five study-quality criteria) and for cost-utility analyses (CUAs) of CIM. It is not surprising that CUA's quality is higher. They generally involve more effort than other cost-effectiveness analyses and are required or recommended by various national guidelines.[73-76] Nevertheless, it seems as though the quality of CUAs of CIM is generally comparable to, or slightly better than, that seen in CUAs across all medicine, at least in

terms of the Tufts quality score, disclosure of funding sources, and the five items where comparable data are available.[77 78]

The number of full evaluations meeting each of the five study-quality criteria are: comparison to usual care 97 (85%), all costs from a recognized perspective 96 (84%), health outcomes from a randomized or matched-control trial 86 (75%), patient-specific data on both costs and outcomes 105 (92%), and sensitivity analyses 37 (32%). Sixty-two (54%) of full evaluations met the first four of these and 31 (27%) met all five. A summary of the results of these 31 higher-quality articles (covering 28 different studies) is shown in Table 4.[54 60 62 68 71 79-104] Twenty-two of these articles (19 of the studies) reported resource use (trials) or model parameters (models) separate from unit prices—a minimum measure of study transferability.[54 62 68 71 79 81-86 88-94 96 101 102 105] For those studies which included a randomized trial, the modified Jadad scores ranged from 2 to 4 on a scale from 0 to 4. The Tufts CEA Registry quality scores for the studies containing a CUA ranged from 4 to 6.5 on a scale from 1 to 7. The percent of the applicable items on the BMJ checklist met by these studies ranged from 66 to 97 percent.

Of the 56 comparisons made in these studies, 16 (29%) are cost-saving—i.e., the added CIM therapy had better health outcomes and lower costs than usual care alone. Cost savings were seen for acupuncture alone (instructional visits with an acupuncturist followed by home self-care by the partner for pregnant women with breech presentations at 33 weeks in terms of reductions in both breech presentation at birth and ceasareans in the Netherlands,[92] and treatment by Traditional Chinese Medicine-trained licensed acupuncturists in private acupuncture clinics in the UK for low back pain in terms of quality-adjusted life-years or QALYs from the societal

perspective[86]) and in combination with other therapies (along with manual therapy, injections and other pain management for patients referred to an orthopedic surgeon's office in Scotland who were unlikely to need surgery in terms of both improvements in health-related quality of life and QALYs[54]). Cost savings were also seen for manual therapy delivered by a physiotherapist, who is also a registered manual therapist, for neck pain in terms of perceived recovery, pain, neck disability, and QALYs[83]; for pre-operative oral supplementation with arginine and omega-3 fatty acids for patients with gastrointestinal cancer undergoing surgery[103]; for vitamin K_1 supplementation for postmenopausal women with osteopenia and osteoporosis in terms of QALYs[105]; for supplementation with vitamins C and E and beta-carotene for cataract prevention[91]; for fish oil supplementation in men with a history of heart attack[88]; for tai chi to prevent hip fractures in nursing home residents[96]; and for naturopathic care offered through a worksite clinic for chronic low back pain in terms of both reductions in absenteeism and gains in QALYs.[81]

Of the 28 cost-utility comparisons, one (massage for low back pain[62]) was dominated—i.e., had worse health outcomes and higher costs than usual care. Five (18%) are cost saving,[54 81 83 86 105] 5 (18%) have incremental cost-effectiveness ratios (ICERs) between $0 and $10,000 per quality-adjusted life-year (QALY),[68 71 82 86 98] and 89 percent had ICERs less than $50,000/QALY, a threshold often considered to represent the upper limit of society's value for a QALY.[106] The cost-saving cost-utility studies were included in the paragraph above (i.e., those that mention QALYs). The studies with cost-utility ICERs between $0 and $10,000 per QALY were: treatment by Traditional Chinese Medicine-trained licensed acupuncturists in private acupuncture clinics in the UK for low back pain in terms of quality-adjusted life-years or

QALYs from the payer perspective,[86] hospital-based acupuncture by licensed Oriental medical doctors in South Korea for 60 year-old women with first-time acute low back pain,[82] acupuncture from physicians with at least 140 hours of training (A-diploma) in Germany for patients with dysmenorrhea,[98] osteopathic spinal manipulation by a general practitioner who is a registered osteopath in the UK for patients with subacute back pain,[71] and an exercise program plus spinal manipulation from a chiropractor, osteopath, or physiotherapist at a private or National Health Service site in the UK for low back pain.[68] The average percent of applicable *BMJ* checklist items met by each study was slightly lower for those studies with at least one cost-saving comparison (85% versus 88%), but the difference was not statistically significant (t-test=0.75, p-value=.460).

Discussion

This comprehensive systematic review identified 338 economic evaluations of complementary and integrative medicine (CIM); 204 of which were published recently (2001-2010) covering a wide range of CIM therapies for a variety of populations. Although most patients who use CIM use more than one modality[35] and despite the attention given to integrative medicine (coordinated access to conventional medicine and CIM),[107] this systematic review found only one study that examined the effects of use of multiple CIM practitioners.[52] In general, the quality of the recent full economic evaluations has held constant and is in line with what is seen in economic evaluations in conventional medicine. Details of the 31 recent higher-quality full economic evaluations indicate potential cost-effectiveness and cost savings across a variety of CIM therapies applied to different conditions. Due to the non-generalizable nature of economic evaluations, the cost estimates shown are specific to their study settings.[40] However, 22 articles

provided at least the minimum information for study transferability. Therefore, their results could be adapted via modeling to determine the economic impact of these interventions in other settings.

The strengths of this study are the comprehensive search strategy, which revealed a substantial number of published economic evaluations of CIM, the use of two reviewers, and the use of multiple measures of study quality. Higher-quality studies were identified and highlighted for policy makers using a simple objective list of quality criteria, which reduced the potential for bias. The weaknesses of this study are similar to those of the other systematic reviews. The reviewers were not blinded to journals and article authors, which may have influenced results. Also, some aspects of what makes a quality economic evaluation could not be judged from what was reported. For example, ideally, pragmatic trials enroll patients typical of normal caseload in typical settings with typically-trained and experienced practitioners following them under routine conditions.[37p251] Judgments as to whether these criteria were met were not always possible from the reports, and were beyond the scope of this review. Finally, publication bias was not assessed. However, since the major goal of this study was to establish the extent of the published literature on this topic and to highlight the results of the higher-quality studies, it is not clear that publication bias is relevant here.

The number of economic evaluations of CIM found and reviewed by this study far exceeds the numbers found in previous studies.[11 19-21 23] This study found a total of 338 economic evaluations of CIM published between and including 1979 and 2010; 211 of these were full economic

evaluations. White and Ernst [19] identified 34 economic evaluations of CAM published 1987-1999; 11 of which were full economic evaluations. Between 1999 and October 2004, Herman et al[20] identified 56 economic evaluations of CAM (39 full evaluations). Between 1994 and May 2004 Hulme and Long[21] identified 19 full economic evaluations of CAM, and over a similar period (1995-2007) Doran et al[23] found 43 economic evaluations (15 full evaluations). Maxion-Bergemann et al[11] identified five (one full) economic evaluations over an unspecified search period. The large number of economic evaluations found in this study reflects the facts that: 1) all evaluations from previous reviews were included; 2) a number of studies have been published since the last search dates of prior reviews; and 3) a more extensive search strategy was used. It should be noted that 20 percent of the articles (68 of 338) in this review were identified through bibliography searches and from expert lists. Therefore, even the application of a long list of search terms to multiple databases does not guarantee that all CIM studies will be identified. However, there is some evidence that the indexing of these articles in medical databases is improving; studies from bibliographies and expert lists made up 32 percent of found articles published 2000 and before, but only 12 percent more recent articles.

There are several implications of this study for policy makers, clinicians, and future researchers. First, there is a large and growing literature of quality economic evaluations in CIM. However, although indexing is improving in databases, finding these studies can require going beyond simple CIM-related search terms. Second, the results of the higher-quality studies indicate a number of highly cost-effective, and even cost saving, CIM therapies. Almost 30 percent of the 56 cost-effectiveness, cost-utility and cost-benefit comparisons shown in Table 4 (18 percent of the CUA comparisons) were cost saving. Compare this to 9 percent of 1433 CUA comparisons

found to be cost saving in a large review of economic evaluations across all medicine.[108] Third, by meeting the five study quality criteria, the studies shown in Table 4 can each be considered a reasonable indicator of the health and economic impacts of the CIM therapy studied, at least in that population and setting. These studies, especially those showing cost savings, should be considered further for applicability in other settings. This requires the study to be transferable.[39] Fortunately, the majority of the higher-quality studies met our measure of study transferability—resource use or model parameters, and unit costs were reported separately.

Given the substantial number of economic evaluations of CIM found in this comprehensive review, even though it can always be said that more studies are needed, what is actually needed are better quality studies—both in terms of better study quality (to increase the validity of the results for its targeted population and setting) and better transferability (to increase the usefulness of these results to other decision makers in other settings). Therefore, the following recommendations are made.

1. That all studies measuring the effectiveness of CIM at least consider also measuring input costs and economic outcomes.
2. That at least one arm of the study be some version of commonly available ("usual") care, and that usual care and all interventions studied be described in sufficient detail that decision makers in other settings can determine what was done and whether the study's usual care comparator is applicable in their setting.
3. That consideration be given to how CIM is typically used (e.g., multiple CIM therapies) or can be used (e.g., coordinated integrative care models) when designing studies.

4. That changes in resource use be reported separately from unit costs in economic evaluations alongside clinical trials and that model parameters and unit costs be clearly reported in decision-analytic modeling studies.
5. That all economic evaluations contain sensitivity analyses to increase the reliability of results.
6. That more consideration be given to modeling as a method to estimate economic outcomes for existing effectiveness trial results, and to generalize existing quality economic evaluation results to other jurisdictions.

Licensure

Declaration of competing interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare: funds from the Bernard Osher Foundation

supported a portion of DME's time on the submitted work; no other support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions

PMH conceived of the idea for the paper, designed the search strategy, reviewed the references found, extracted the data from each included article, and is the guarantor for this study. In parallel, BLP also reviewed the references found, extracted data from included articles, and worked with PMH to resolve any discrepancies between reviewers. CMW provided practical insight and an international perspective to the design of the paper and interpretation of results. DME participated in the early design of the study, including the data extraction plan, inclusion/exclusion criteria, and the interpretation of results. All authors contributed to the drafting and editing of the manuscript.

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No ethical approval was required as this is a review of published work.

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Data sharing statement

The full list of found articles is available in a Word document from the corresponding author.

PRISMA statement

The manuscript was prepared following the PRISMA guidelines. A PRISMA checklist is included as a supplemental file.

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Table 1. Types of full economic evaluations

	Cost-benefit analysis (CBA)	Cost-effectiveness analysis (CEA)	Cost-utility analysis (CUA) (a special case of CEA)
Unit of health outcome	Monetary units (e.g., US dollars)	Natural units (e.g., life-years gained)	Units of overall impact on length and quality of life (e.g., quality-adjusted life-years, QALY)
Results	Net benefits $(B_1-B_2) - (C_1-C_2-S_1+S_2)$	Cost-effectiveness ratio* $(C_1-C_2-S_1+S_2)/(E_1-E_2)$	Cost-utility ratio* $(C_1-C_2-S_1+S_2)/(QALY_1-QALY_2)$

* Ratios are calculated when both the costs and the effects (health improvements) of one therapy alternative are higher than those of another. When the costs are lower and the effects are better for one therapy, it is said to dominate the alternative (and the alternative is said to be dominated) and no ratio is presented. B1 = monetary value of health outcomes of alternative 1; B2 = monetary value of health outcomes of alternative 2; C1 = total input costs of alternative 1; C2 = total input costs of alternative 2; S_1 = total cost savings (economic outcomes) for alternative 1; S_2 = total cost savings (economic outcomes) for alternative 2; E1 = health effects of alternative 1; E2 = health effects of alternative 2; QALY1 = quality-adjusted life-years of alternative 1; QALY2 = quality-adjusted life-years of alternative 2.

Table 2. Types of individual complementary and integrative medicine (CIM) therapies studied for various conditions and in various populations: 2001-2010 (reported as the ratio of the total number of economic evaluations to the number of full economic evaluations)

	Manipulative and body-based practices	Acupuncture	Natural Products	Other Mind-body medicine	Homeopathy	CIM in general	Other CIM therapies*	TOTALS†
Back pain	28:19	11:10	2:2	-	1:1	3:0	2:2	42:29
Rheumatic disorders	9:5	6:4	6:6	2:2	-	1:0	4:3	27:19
Mixed populations	4:1	6:1	2:1	3:1	9:5	2:1	3:2	24:9
Cardiovascular disease and diabetes	-	1:0	8:6	6:4	1:1	-	3:1	18:12
Infection (various)	-	-	6:4	-	7:4	-	-	13:8
Surgery	1:1	2:2	4:3	5:4	-	-	-	12:10
Members of insurance plans	3:0	2:0	-	-	1:0	7:0	-	12:0
Mental disorders	-	2:2	-	5:3	1:1	1:0	2:0	11:6

(various)								
Older populations	-	-	6:3	2:0	-	-	3:1	11:4
Headaches	1:0	3:3	-	4:3	1:1	-	-	9:7
Children (various conditions)	1:0	-	-	-	6:4	1:0	1:0	9:4
Cancer	2:1	2:1	1:1	2:2	-	2:0	-	8:4
Pregnancy and women's health	-	5:5	1:0	1:0	-	-	-	7:5
Allergies	-	1:1	-	-	3:1	-	1:1	5:3
Other conditions‡	1:1	1:1	3:3	5:4	2:1	2:0	6:2	19:11
TOTALS†	45:25	41:29	38:28	27:16	24:13	18:1	25:12	204:114

* Other CIM therapies included aromatherapy, healing touch, Tai Chi, Alexander technique, spa therapy, music therapy, electrodermal screening, clinical holistic medicine, naturopathic medicine, anthroposophic medicine, water-only fasting, Ornish Program for Reversing Heart Disease, use of a corset, and use of a traditional mental health practitioner.

† Totals across (down) columns will not add to numbers in the totals column (row) due to individual studies addressing more than one CIM therapy (patients in more than one group).

‡ Other conditions studied included patients with multiple chemical sensitivities, respiratory disease, pharyngeal dysphagia, dyspepsia, functional bowel disorders, other functional disorders, venous leg ulcers, major burns, and constipation; patients who rated themselves as physically ill or having low quality of life; patients in home hospice or with home nursing; long-term care workers; and prisoners.

Table 3. Comparison of various quality measures between economic evaluations of complementary and integrative medicine (CIM) and conventional medicine

	Economic evaluations of CIM					CUAs across all medicine*	
	All Full n=114	2001-2005 n=59	2006-2010 n=55	Higher quality n=31	CUAs n=27	1998-2001 n=300	2002-2005 n=637
Average % met of applicable items on *BMJ* checklist	72%	71%	73%	87%	89%		
Presented the study perspective clearly	61%	58%	64%	87%	93%§	74%	83%§
Presented the study time horizon	96%	98%‡	93%‡	100%	100%‡	75%	87%‡
Conducted and reported sensitivity analysis	32%	22%§	44%§	100%	93%§	93%	84%§
Discounted costs and health effects, where appropriate#	60%	25%‡	76%‡	94%	100%‡	85%	84%‡
Stated year of currency for resource costs	59%	54%	60%	77%	78%§	83%	85%§
Separate reporting of resource use (trials), parameters (models), and unit costs (for transferability)	52%	51%	53%	71%	70%		
Disclosed funding sources	72%	58%‡	76%‡	84%	93%‡	65%†‡	
Industry sponsored	10%	12%	11%	10%	7%	18%†	
Average Tufts quality score (CUAs only)					4.75¶	4.25†¶	

* Data from Table 3 in Neumann PJ. Costing and perspective in published cost-effectiveness analysis. *Medical Care.* 2009;47(Suppl 1):S28-S32.

† Data from Table 3 in Neumann PJ, Greenberg D, Olchanski NV, Stone PW, Rosen AB.Growth and quality of the cost-utility literature, 1976-2001. *Value in Health* 2005;8(1):3-9. Industry sponsored was calculated as a percent all studies 1976-2001.

‡χ^2 test p-value<.001; §χ^2 test p-value<.01; ¶t-test p-value=.002; Comparisons were made between CIM economic evaluations published 2001-2005 and those published 2006-2010, and between CUAs of CIM 2001-2010 and CUAs of all medicine 2002-2005.

Denominators for the percentages reported in this row are the number of studies which evaluated impacts past one year in either the base case or in sensitivity analyses. For the first five columns the denominators are 25, 8, 17, 16, and 11, respectively. This information was not available for the last two columns.

CUA = cost-utility analysis

Table 4. Summary of results of complementary and integrative medicine (CIM) economic evaluations that met five study quality criteria (31 articles representing 28 studies)

	CIM Therapy Compared to Usual Care Alone*	Treatment duration / Study duration	Patient Population	Primary Outcome(s)	Setting (information often limited by what was reported)	Sample Size	Study design and quality scores†	Resource Use (Trials), Parameters (Models), and Unit Costs (Both) Reported Separately?	Form and Perspective of Economic Evaluation	Incremental Cost-Effectiveness Ratio (2011 USD)‡
Acupuncture studies										
Brown et al (2001) *Health Bull*	Adjunctive acupuncture, manual therapy, injections and other pain management	Up to 1 year / 1 year	Patients referred for an orthopedic outpatient consultation who were classified as unlikely to require surgery	Clinical: SF-36 and, if appropriate, Aberdeen Low Back Pain Scale or Edinburgh Knee Function Scale; Economic: EQ5D	Individualized care from one "physical medicine" physician in a hospital outpatient clinic in Scotland	829	R (2) 81% BMJ	Yes	CEA – H CUA – H	Cost saving Cost saving

van den Berg et al. (2010) *Complement Ther Med*	Adjunctive breech version acumoxa	2 visits / From 33 weeks to delivery	Pregnant women with breech presentation at 33 weeks	Economic: percent of breech presentations at delivery – two "main analyses" – with and without the option of external cephalic versions	2 instructional visits to an acupuncturist followed by daily home self-care Netherlands	NA	Decision tree model 81% BMJ	Yes	CEA – P CEA – P	Cost savings Cost savings
Ratcliffe et al. (2006) *BMJ* and Thomas et al. (2005) *Health Tech Assess*	Adjunctive acupuncture	3 months / 2 years	Patients with low back pain	Clinical: Bodily pain fm SF-36; Economic: QALYs fm SF-6D	Up to 10 treatments from a TCM-trained acupuncturist in acupuncture clinic in UK	239	R (3) Tufts 5 94%/94% BMJ	Yes	CUA – S CUA – P	Cost saving $8755/QALY

Kim et al. (2010) *BMC CAM*	Adjunctive acupuncture	10 treatments in 3 month cycles / 5 years	60-year-old females with 1st time acute low back pain	Clinical: Roland-Morris Disability, Symptom bothersomeness; Economic: QALYs fm literature	Hospital-based licensed Oriental medical doctors in South Korea	NA	Markov model Tufts 4.5 94% BMJ	Yes	CUA – S	$3086/QALY
Witt et al. (2008) *Am J Obs Gyn*	Adjunctive acupuncture	3 months / 6 months	Patients with dysmenorrhea	Clinical: Pain Intensity VAS; Economic: QALYs fm SF-6D	Up to 15 sessions with a physician trained in acupuncture (A-diploma) in Germany	201	R (3) Tufts 5.5 77% BMJ	No	CUA – S	$4708/QALY§

Witt et al. (2006) *Am J Epidemiol*	Adjunctive acupuncture	3 months / 6 months	Patients with chronic low back pain	Clinical: Hannover Functional Ability Questionnaire; Economic: QALYs fm SF-6D	Up to 15 sessions with a physician trained in acupuncture (A-diploma) in Germany	2,518	R (3) Tufts 4.5 73% BMJ	No	CUA – S	$16,230/QALY§
Witt et al. (2008) *Cephalalgia*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with headache	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	3,182	R (2) Tufts 5.5 88% BMJ	No	CUA – S	$18,225/QALY§
Willich et al. (2006) *Pain*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with chronic neck pain	Clinical: Neck Pain and Disability Scale; Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	3,451	R (2) Tufts 5 88% BMJ	No	CUA – S	$19,226/QALY§

Wonderling et al. (2004) *BMJ* and Vickers et al. (2004) *Health Tech Assess*	Adjunctive acupuncture	3 months / 1 year	Patients with chronic headache	Clinical: headache severity score; Economic: QALYs fm SF-6D	Acupuncture-trained physio-therapists in own clinics in UK	401	R (3) Tufts 5 97% / 93% BMJ	Yes	CUA – S CUA – P	$19,785/QALY $21,074/QALY
Reinhold et al. (2008) *Eur J Health Econ*	Adjunctive acupuncture	3 months / 3 months	Patients with chronic hip or knee osteoarthritis	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma), Germany	489	R (3) Tufts 4 87% BMJ	No	CUA – S	$27,900/QALY§
Witt et al. (2009) *Am J Epidemiol*	Adjunctive acupuncture	Up to 15 treatments / 3 months	Patients with allergic rhinitis	Economic: QALYs fm SF-6D	10-15 sessions with physician trained in acupuncture (A-diploma) in Germany	981	R (3) Tufts 4 94% BMJ	No	CUA – S	$28,137/QALY§
Manipulative and body-based practices – See also Brown et al, 2001, above.										

Korthals-de Bos et al. (2003) *BMJ*	Manual therapy	6 weeks / 1 year	Patients with neck pain	Clinical: Perceived recovery, pain VAS, and Neck Disability Index; Economic: All clinical plus QALYs fm EQ-5D	Up to 6 weekly 45 min sessions with a physiotherapist who is also a registered manual therapist in the Netherlands	183	R (3) Tufts 6.5 83% BMJ	Yes	CEA – S CEA – S CEA – S CUA – S	Cost saving Cost saving Cost saving Cost saving
Williams et al. (2004) *Fam Pract*	Adjunctive osteopathic spinal manipulation	2 months / 6 months	Patients with subacute (2-12 week) back pain	Clinical: Extended Aberdeen Spine Pain Scale; Economic: QALYs fm EQ-5D	3 or 4 sessions with a general practitioner who is a registered osteopath at own clinic in UK	187	R (3) Tufts 5 89% BMJ	Yes	CUA – P	$8730/QALY

UK BEAM Trial Team. (2004) *BMJ*	Adjunctive spinal manipulation and exercise	3 months / 1 year	Patients with low back pain	Economic: QALYs fm EQ-5D	8 sessions with a chiropractor, osteopath, or physiotherapist at a private or NHS site in UK	1,287	R (3) Tufts 6 93% BMJ	Yes	CUA – P	$8425/QALY
	Adjunctive spinal manipulation								CUA – P	$10,642/QALY
Hollinghurst et al. (2008) *BMJ* [1]Compared to usual care plus exercise	Alexander technique	6 lessons / 1 year	Patients with chronic or recurrent non-specific back pain	Clinical: Roland-Morris Disability Questionnaire (RMDQ); Economic: Above plus QALYs fm EQ-5D	Alexander technique teachers and massage therapists at own locations in UK	579	R (3) Tufts 5.5 97% BMJ	Yes	CUA – P CEA – P	$13,300/QALY $255/RMDQ pt
	Alexander technique plus exercise[1]	6 lessons / 1 year							CUA – P CEA – P	$12,022/QALY $144/RMDQ pt
	Massage	6 sessions / 1 year							CUA – P CEA – P	Dominated $1010/RMDQ pt
	Massage plus exercise[1]	6 sessions / 1 year							CUA – P CEA – P	$11,959/QALY $354/RMDQ pt
Haas et al. (2005) *J Manip Physiol Ther*	Treatment in a chiropractic clinic	Un-specified /	Patients with acute low back pain	Clinical and Economic: pain severity 100mm	Doctors of Chiropractic in	1,943	MC 66% BMJ	No	CEA – P	$21/pain mm

		1 year	Patients with chronic low back pain	VAS and Revised Oswestry Disability Questionnaire	own clinics in Oregon, USA	837			CEA – P	$0.73/pain mm
Natural products										
Braga, et al. (2005) *Nutrition*	Adjunctive pre-operative arginine and omega 3 fatty acid supplementation	5 days / 5 days plus hospital stay	Patients with gastrointestinal cancer undergoing surgery	Economic: percent of patients without complications	12.5g arginine, 3.3g omega 3 fatty acids, and 1.2g RNA in liquid daily taken orally for 5 days before surgery, Italy	204	R (3) 88% BMJ	No	CEA – H	Cost saving

Stevenson et al. (2010) *Med Decis Making* and Stevenson et al. (2009) *Health Technol Assess*	Vitamin K1	10 years / 10 years	Postmenopausal women with osteoporosis/ osteopenia	Clinical: Osteoporotic fracture Economic: QALYs fm the literature	10mg/d of vitamin K1 daily, UK	NA	Patient-level simulation model Tufts 4.5 81% / 84% BMJ	Yes	CUA – P	Cost saving
Trevithick et al. (2006) *J Orthomol Med*	Adjunctive antioxidants (vitamins C and E and beta-carotene)	25 years / 25 years	Cohort of Ontario residents aged 50-54 (prevention of cataracts)	Clinical: cataract formation	750mg/d vitamin C, 600mg/d vitamin E, & 18mg/d beta-carotene daily, Canada	NA	Markov-type cohort model 79% BMJ	Yes	CEA – P	Cost saving
Schmier et al. (2006) *Manag Care*	Adjunctive omega 3 fatty acid supplementation	42 months / 42 months	Males with a history of a heart attack	Economic: fatal MIs and cardiovascular deaths	"fish oil pills," USA	NA	Decision analytic model 77% BMJ	Yes	CEA – S CEA – P	Cost saving $11,903/fatal MI avoided

Lamotte et al. (2006) *Pharmacoecon*	Adjunctive omega-3 polyunsaturated fatty acids	3.5 years / Lifetime	Patients after an acute myocardial infarction	Economic: life-years saved	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, Australia, Belgium, Canada, Germany and Poland	NA	Decision tree model 89% BMJ	Yes	CEA –P CEA –P CEA –P CEA –P CEA –P	$5413/LYG Australia $8184/LYG Belgium $4476/LYG Canada $6750/LYG Germany $7747/LYG Poland
Quilici et al. (2006) *Int J Clin Pract*	Adjunctive omega-3 polyunsaturated fatty acids	4 years / Lifetime	Patients after an acute myocardial infarction	Economic: life-years gained (LYG), QALYs fm the literature, deaths avoided	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, UK	NA	Markov model Tufts 5 93% BMJ	Yes	CEA –P CUA – P	$28,420/LYG $35,940/QALY

Franzosi et al. (2001) *Pharmacoecon*	Adjunctive omega-3 poly-unsaturated fatty acids	3.5 years / 3.5 years	Patients with recent myocardial infarction	Clinical: death and non-fatal MI or stroke; Economic: life-years gained (LYG)	~465mg EPA & ~385mg DHA ethyl esters in a daily gelcap, Italy	5,664	R (4) 85% BMJ	No	CEA – P	$41,867/LYG
Black et al. (2009) *Health Technol Assess*	Adjunctive glucosamine sulfate	22.6 years / 22.6 years	Patients with osteoarthritis of the knee	Clinical: Pain, function, joint space loss Economic: QALYs fm the literature	Glucosamine sulfate powder 1500mg daily in oral solution, UK	NA	Cohort simulation model 84% BMJ	Yes	CUA-P	$59,053/QALY
Other complementary and integrative medicine therapies										
Wilson and Datta. (2001) *J Clin Outcomes Manag*	Adjunctive yang-style tai chi	1 year / 1 year	Nursing home residents at average risk for a fall	Economic: hip fractures avoided	2 classes/week monitored by a certified tai chi instructor & an assistant, USA	NA	Decision tree model 96% BMJ	Yes	CEA – P	Cost saving

Herman et al. (2008) *Altern Ther Health Med*	Adjunctive naturopathic care including acupuncture, relaxation exercises, dietary and exercise advice	3 months / 6 months	Patients with chronic low back pain	Clinical: Oswestry Disability Questionnaire; Economic: QALYs fm SF-6D	Twice weekly visits to licensed naturopathic doctors also trained in acupuncture in a worksite clinic in Canada	70	R (3) Tufts 5 96% BMJ	Yes	CUA – S CEA – E CBA – E	Cost saving $191/absentee day avoided Cost saving

Van Tubergen et al. (2002) *Arthritis Rheum*	Combined spa-exercise therapy	3 weeks / 40 weeks	Patients with ankylosing spondylitis	Clinical: Bath Ankylosing Spondylitis Functional Index (BASFI 10pts), pain VAS, well-being VAS, and morning stiffness in minutes; Economic: Above plus QALYs fm EQ-5D	3-week stay at one of two spa-resorts with therapy provided by trained physio-therapists, Netherlands	120	R (3) Tufts 4.5 90% BMJ	Yes	CEA – S CEA – S CUA – S CUA – S	$2159/BASFI pt (spa in Austria) $4215/BASFI pt (spa in the Netherlands) $12,703/QALY (spa in Austria) $31,609/QALY (spa in the Netherlands)
Zijlstra et al. (2007) *Rheum*	Adjunctive spa therapy	2.5 weeks / 1 year	Patients with fibromyalgia	Economic: QALYs fm VAS and SF-6D	18-day stay at a spa in Tunisia with a variety of treatments, Netherlands	128	R (3) Tufts 4 97% BMJ	Yes	CUA – S CUA – S	$46,443/QALY (VAS) $92,886/QALY (SF-6D)

* The use of the term "adjunctive" in this column indicates CAM therapies used in addition to usual care for that condition unless otherwise indicated.

† Study design: R = randomized, MC = matched controls and/or results statistically adjusted for baseline differences. A modified Jadad score (maximum score = 4) is provided if the study was randomized. If the study was a CUA and a quality score was available from the Tufts Medical Center Institute for Clinical Research and Health Policy Studies CEA Registry (https://research.tufts-nemc.org/cear/Default.aspx), it is

reported. Quality scores range from 1 to 7 with 7 representing the highest quality. The last number is the percent of the applicable items on the BMJ 35-item quality checklist that this study met. If a study had more than one publication, both percentages were reported. The BMJ checklist is found in Drummond MF, Jefferson TO, BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. BMJ 1996;313:275-283.

‡ The costs reported in each study were first converted to US dollars (USD) using the Federal Reserve annual exchange rate (http://www.federalreserve.gov/releases/g5a/20090102/, accessed Jan 30,2012) for the study's currency year and then inflated to 2011 values using the medical care component of the Consumer Price Index (http://www.bls.gov/cpi/cpi_dr.htm#2007, accessed Jan 30, 2012). In comparisons labeled as cost saving the CIM therapy both improved health and lowered costs compared to usual care. In the comparison labeled dominated the CIM therapy had worse health outcomes and higher costs than usual care.

§ These studies did not report a currency year so it was estimated as being one year prior to publication.

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; CBA=cost-benefit analysis.

P = Payer perspective; S = Societal perspective; E = Employer perspective; H = Hospital perspective

QALY = quality-adjusted life-year; VAS = visual analog scale

Figure legends

Figure 1. The flow of records and articles through the systematic review

PRISMA 2009 Flow Diagram